

# Variations in Long-Term Opioid Therapy Definitions: A Systematic Review of Observational Studies Using Routinely Collected Data (2000–2019)

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October 5, 2020

## Abstract

Routinely collected data has been increasingly used to evaluate and monitor long-term opioid therapy (LTOT) patterns, with very little guidance on how to measure LTOT from these data sources. We conducted a systematic review of studies published between Jan 2000 and Jul 2019 to catalogue LTOT definitions, the rationale for definitions, and LTOT rates in observational research using routinely collected data in non-surgical settings. We screened 4,056 abstracts, 209 full-text manuscripts and included 126 studies; mostly from the US (82%) and published between 2015 and 2019 (68%). We identified 78 definitions of LTOT, commonly operationalised as 90 days of use within a year (21%). Studies often used multiple criteria to derive definitions (63%), mostly based on measures of duration, such as supply days/days of use (67%), episode length (21%), or prescription fills within specified time periods (9%). Definitions were based on previous publications (63%), clinical judgment (17%), or empirical data (3%); 10% of studies applied more than one definition. LTOT definition was not provided with enough details for replication in 14 studies and 37 studies did not specify the opioids evaluated. Rates of LTOT ranged from 0.2% to 57% according to study design, population and definition used. We observed a substantial rise in studies evaluating LTOT with large variability in the definitions used and poor reporting of the rationale and implementation of the definitions. This variation impacts on research reproducibility, comparability of findings and the development of strategies aiming to curb therapy that is not guideline-recommended.

## INTRODUCTION

The increasing availability of opioid analgesics has been accompanied by an alarming rise in opioid misuse and related harm. Worldwide, opioid utilisation increased 2.5-fold between 2001-03 and 2011-13,<sup>[1]</sup> with the United States and Canada having the largest per capita opioid consumption. Opioid-related deaths rose more than 20% in developed countries in the same period. In 2018, 46,800 people died due to opioid overdoses in the United States with 32% involving prescription opioids.<sup>[2, 3]</sup>

Opioid analgesics were initially introduced to manage acute and cancer-related pain and subsequently registered to treat chronic noncancer pain (CNCP).<sup>[4]</sup> Short-term opioid use for CNCP has limited to moderate clinical benefit<sup>[5, 6]</sup> and there is limited evidence of long-term effectiveness.<sup>[5, 7, 8]</sup> Prolonged opioid use has been associated with adverse events, hospitalisations, dependence and overdose.<sup>[9-12]</sup> Therefore, guidelines for CNCP encourage initiating therapy with low-doses and limiting treatment to no more than eight to 12 weeks.<sup>[9, 13]</sup>

Routinely collected data and drug monitoring programs, using dispensing claims and prescribing data, represent a rich source of information supporting large-scale population-based research to quantify, monitor and develop evidence-informed strategies to reduce long-term opioid therapy (LTOT). However, translating guideline recommendations to measurement in routinely collected data can be challenging. Despite the growing literature of opioid use and harms, there is no gold standard definition of LTOT for use in routinely collected data.

Recent systematic reviews have identified between 29 and 41 variants of definitions.<sup>[14, 15]</sup> These studies did not focus exclusively on definition applied to routinely collected dispensing and prescribing data. Rather they included studies ascertaining opioid use across a broad spectrum of methods including surveys. They also focused mostly on the use of opioids in surgical settings and did not shed light on the rationale for the various definitions operationalised in the studies.

Understanding the terminologies and definitions currently in place in observational research is crucial for planning research, evaluating findings, and informing evidence-based recommendations. Given the increasing role of routinely collected data to evaluate opioid use and outcomes, especially for CNCP management, we aimed to catalogue the definitions and terminology relating to LTOT, the rationale for definitions, and LTOT rates in observational research using routinely collected data in non-surgical settings.

## METHODS

### Study identification

We searched MEDLINE and EMBASE online databases using a combination of keywords, MeSH headings, and words commonly used to describe LTOT, such as persistent or chronic use of opioids. The search strategy was undertaken after consultation with the information specialist of UNSW Sydney library in July 2018 and updated in August 2019 (see Supplementary Appendix A). We also conducted a manual search of the references of included studies and published systematic reviews for any additional articles not captured by our search strategy.

### Study eligibility criteria

We included full-text English-language studies evaluating LTOT as an exposure or outcome in observational studies using routinely collected data published between January 2000 and July 2019.

We excluded studies according to design (e.g., systematic reviews, clinical trials, editorials, abstracts), medicine use (e.g., studies evaluating other analgesics), population (studies conducted exclusively among populations <18 years old) and setting (those focusing on opioids use for surgery) and those who did not provide any detail of how LTOT was measured.

### Study selection and data extraction

Two reviewers (JOC, NB) independently screened titles, abstracts and read the full text of eligible studies to identify relevant studies for inclusion. Disagreements were resolved by a third reviewer (SAP). Pairs of reviewers extracted data from all included studies and disagreements were resolved by discussion. We extracted the following study features:

- Study characteristics: first author and publication year, publishing journal, study design, setting.
- Study period: observation period (beginning and end year of observation).

- Data source (s): initial data source to ascertain opioid use, classified as prescribing records or pharmacy dispensing data; the extent of population coverage of the data source used (e.g., local, regional or nationwide); and other sources of data used in the study (e.g., medical records, surveys).
- Study population: the size of the study population, overall and per groups compared; the age of included subjects, classified as adults (18 years or older), elderly (65 years or older), all age groups (no age restrictions) and other; inclusion and exclusion criteria for study participation and health conditions evaluated.
- LTOT measures:
- Terminology related to LTOT definition, such as ‘Chronic’ or ‘Persistent’.
- LTOT definition, classified as A) duration measures (supply days or days of use, length of the opioid use episode, prescription fills within specified time periods) and B) additional measures (number of prescriptions or fills, opioid dose, continuous use of opioids, or other criteria). Opioid dose is generally measured by Defined Daily Doses (DDD) or Oral Morphine Equivalents (OME)<sup>[16]</sup> and continuous use of opioids is commonly measured by assessing consecutive days or months of opioid use or a lack of a defined gap period between prescriptions.
- Rationale supporting LTOT definition and whether studies used more than one LTOT definition.
- Rates of LTOT and the denominator used in the estimate (e.g., whole population, healthcare enrollees, people using opioids, people with specified health conditions).

## Reporting

We evaluated 31 relevant items pertaining to the REporting of studies Conducted Observational Routinely-collected health Data (RECORD) checklist<sup>[17]</sup> as a method of evaluating the completeness of study reporting (see Supplementary Appendix B). We calculated the completeness score, based on RECORD checklist, as the percentage of items meeting the specified criteria in relation to the overall applicable items for each study, with scores closer to 100% indicating a more comprehensive reporting. Two reviewers (JOC, CB) independently scored a sample of 20% of studies and disagreements were resolved by discussion. Since we obtained a substantial Kappa agreement ( $k = 0.87$ ),<sup>[18, 19]</sup> one reviewer (JOC) scored the remainder.

## Analysis

We conducted a descriptive analysis of studies and presented key findings in tables and figures developed using the R Foundation for Statistical Computing Program 3.6.0 version (R Core Team 2017, Vienna, Austria).

## RESULTS

Our electronic search yielded 4,056 studies, with an additional 9 studies identified through manual searches. After removal of duplicates, we screened 3,257 titles and abstracts. We assessed 209 full-text manuscripts for eligibility and included 126 studies in this review (Figure 1) (see the Supplementary Appendix C for details of studies features and Appendix D for the list of included studies).

[Figure 1 here]

*Description of included studies (Table 1)* : Most studies were conducted in the United States (103 studies, 82%), followed by Europe (16 studies, 13%), six which were conducted in Norway. The number of studies escalated over time, with 86 studies (68%) published between 2015 and 2019, of which 26 (20.6%) were published in 2019 (Jan-Jul). Cohort studies were the most common (92 studies, 73%), followed by cross-sectional studies (32 studies, 25%).

*Data sources (Table 1):* Data on opioid use was retrieved from pharmacy dispensing records for 108 studies (86%), with almost half (58 studies, 46%) using data from nationwide administrative systems. Pharmacy dispensing claims or prescription records were used with one (70 studies, 56%) or multiple data sources (42 studies, 33%), such as medical health records, medical claims, hospitals separations, surveys, census, and surveillance registries (e.g., mortality, cancer).

*Study Populations (Table 1):* One-quarter of studies did not impose age restrictions, 64% included adults only and 9% focused exclusively on the elderly (aged 65+ years);<sup>[20-30]</sup> two studies focused on adolescents and young adults (13-29 years old).<sup>[31, 32]</sup>

Study populations varied substantially in size, ranging from 121<sup>[33]</sup> to 48 million people.<sup>[34]</sup> One-fifth of studies included only opioid-naïve individuals (27 studies), defined as the absence of opioid use in the six or 12 months prior to the index date. Studies investigated opioid use among patients with various specific health conditions, such as CNCP (42 studies, 33%), musculoskeletal conditions (15 studies, 12%), injuries or trauma (13 studies, 10%) or the infectious diseases HIV or hepatitis C (8 studies, 6%). Six studies (5%) included patients with both cancer pain and CNCP without reporting stratified results<sup>[35-40]</sup> and six studies (5%) evaluated patients with cancer<sup>[26, 41, 42]</sup> or cancer survivors.<sup>[27, 43, 44]</sup>

[Table 1 here]

*LTOT definitions (Figure 2, Table 2) :* Approximately two-thirds of the 126 studies used two or more criteria to define LTOT (80 studies). Definitions were generally based on one measure of opioid duration, such as days of use or supply (84 studies, 67%), episode length (27 studies, 21%) or prescription fills within a specified time period (11 studies, 9%). Additional criteria included the number of fills (56 studies, 44%), continuous use (34 studies, 27%) or other criteria (16 studies, 13%). Only seven studies (6%) considered opioid dosage to derive LTOT definitions.

Overlapping opioid prescriptions were addressed in 22 studies (17%). Twelve studies carried forward supplies occurring before the prior prescription ended, of which seven studies carried forward supplies for a specific number of overlapping days (e.g., < 10 days or 20% of overlapping).<sup>[45-47]</sup> The remaining 10 studies considered overlapping prescriptions as concurrent use.

LTOT definitions were based on previous publications (79 studies, 63%), clinical judgment (21 studies, 17%), or empirical data (4 studies, 3%) and only 12 studies tested more than one definition (10%).

[Figure 2 here]

We identified 78 definitions of LTOT of which ten were used by more than 75% of studies (shown in Table 2). LTOT was most often operationalised as 90 days of cumulative or continuous use within a year (27 studies, 21%). The rationale for this definition is based on clinical judgment and empirical data from the TROUP study,<sup>[48]</sup> showing one-quarter of people using opioids for more than 90 days in a given year received opioids in the subsequent year for more than 180 days. An additional 16 studies (13%) used 90 days of opioid use or supply as a threshold to define LTOT within various follow-up periods.

Another definition based on empirical data and commonly used across studies is derived from the CONSORT study.<sup>[49]</sup> The definition combines the length of opioid use episodes ([?] 90 days) with cumulative days of supply ([?] 120 days) or the number of fills ([?] 10) and was based on an increased probability of patients receiving an additional prescription with 10 days of supply surpassing this threshold. We found 23 studies (18%) operationalised this definition according to the original study or with some adaptation.

The use of opioids for more than 180 days within a year (7 studies, 6%), or within another time frame (4 studies, 3%), was based on clinical judgment to distinguish LTOT from acute use of opioids and on the clinical relevance of extending the use beyond 90 days.<sup>[50, 51]</sup>

Studies that did not evaluate duration of opioid use based on the length of episodes or days of supply often used the number of prescriptions/fills and the distribution of fills within the follow-up period to define LTOT: nine studies (7%) used [?] 3 fills as a threshold in various follow-up windows and six (5%) used [?] 6 fills.

Finally, four studies (3%) applied an LTOT definition developed by Svendsen et al <sup>[52]</sup> that assumes people use opioids at least half of the days of the year (denominated wide definition) and is associated with a higher probability of receiving opioids in the following two years.

[Table 2 here]

*LTOT rates (see the Supplementary Appendix C for details):* LTOT rates varied substantially across studies, ranging from 0.2%<sup>[52]</sup> to 57%<sup>[45]</sup> according to the definition used, study design and population included, denominator, calendar year and follow-up window. Studies testing the impact of different LTOT definitions reported differences in rates ranging from <1 to 38 percentage points (1.4 to 13-fold variation within definitions from the same study).<sup>[24, 26, 52, 59, 79, 99, 123, 126, 128]</sup>

Most commonly, studies reported LTOT rates as a proportion of people with specified health conditions (67 studies, 53%), followed by people using opioids (33 studies, 26%). A lower proportion reported rates among healthcare enrollees (12 studies, 10%), based on the whole population (4 studies, 3%), or using other denominators (e.g., opioid fills, 4 studies, 3%). Finally, six studies (5%) reported multiple rates (e.g. both among people using opioids and the whole population).

Not surprisingly, we observed the lowest rates of LTOT when they related to the entire eligible jurisdictional population, varying from 0.2% in Norway <sup>[52]</sup> to 1.4% in Denmark.<sup>[113]</sup> LTOT ranged from 0.3%<sup>[129]</sup> to 35.8%<sup>[38]</sup> among people who were opioid-naïve and prevalent use ranged between 1.8%<sup>[130]</sup> and 43.0%.<sup>[22]</sup> We also observed significant variation in estimates when they were estimated as a proportion of people with specified health conditions; from 0.5% among young people with CNCP who were opioid-naïve<sup>[31]</sup> to 26.4% among veterans with CNCP, irrespective of prior opioid use.<sup>[72]</sup> LTOT rates ranged from 2.7% to 32.1% among people with different cancers<sup>[27, 42]</sup> and 4.0% to 55.4% among people with infectious diseases.<sup>[33, 75]</sup> Variations among people with neuropathy (8.8%-18.8%)<sup>[56, 77]</sup> and trauma or injuries (1.1%-29.0%) were also observed.<sup>[131, 132]</sup> Among people with musculoskeletal diseases, estimates ranged from ~2.0% for opioid-naïve people with rheumatoid arthritis <sup>[133]</sup> to 41.0% among people with rheumatoid arthritis irrespective of prior opioid use.<sup>[30]</sup>

*Reporting of the included studies – RECORD (Figure 3):*

The median completeness score was 87% (interquartile range 82–92%) and only one study scored 100%. A large proportion of studies did not describe/outline the study design, either in the abstract (56 studies, 45% - Item 1A) or in the methods (37 studies, 29% - Item 4). Despite the fact LTOT definition was stated, 14 studies (11% - Item 7) did not provide enough detail to allow the replication of results or provided inconsistent definitions in the abstract/methods. In addition, 37 studies did not specify which opioids were considered in the analysis (29% - Item 7.1). Other methodological areas of underreporting included how missing data and loss to follow-up were addressed (77 studies and 48 studies, Items 12C and 12D, respectively).

[Figure 3 here]

## DISCUSSION

Our systematic review, based on 126 observational studies using routinely collected data, provides a comprehensive summary of the use and applications of LTOT definitions in observational research. We identified 78 distinct definitions, most of them using a minimum of 90 days of opioid therapy as a threshold for LTOT within a range of follow-up periods, commonly one year. The rationale cited for the use of these definitions was based mostly on previous publications and clinical judgement; a minority of studies used empirical data to derive definitions or tested the impact of using multiple definitions. Moreover, we identified the need to improve reporting on methodological aspects impacting the LTOT definition, such as listing the medicines and formulations included in the analysis, depicting how overlapping prescriptions and missing data were addressed, referring to the follow-up period, and explicitly stating the denominator for LTOT rates.

Whilst our systematic review was not the first to identify variation in LTOT definitions, the focus on routinely collected data and non-surgical settings adds complementary insights to prior systematic reviews.<sup>[14, 15]</sup> A key advantage leveraged from routinely collected data is to facilitate the characterisation of multiple patterns of opioid use based on prescription/dispensing information including its frequency, dose, opioid type and strength.<sup>[14, 52]</sup> As expected, the duration of opioid use, commonly based on supply days, was the most common criteria used to define LTOT (67%) in our systematic review compared to 27%-38% in the previous ones.<sup>[14, 15]</sup> We also observed a higher number of studies using opioid dose (7 vs 0-1 study) to derive LTOT definitions<sup>[14, 15, 134]</sup> and reporting how they accounted for overlapping prescriptions (22 vs 3 studies).<sup>[14]</sup>

Encouragingly, the commonly used threshold of 90 days of opioid therapy observed in this and prior studies<sup>[14]</sup> aligns with guidelines recommendations for opioid trial duration and has been tested on empirical data based specifically on routinely collected data.<sup>[48, 49]</sup> The cumulative number of supply days (i.e., duration of prescriptions filled) has been identified as one of the strongest predictors of LTOT compared to other criteria, such as the number of refills, or OMEs dispensed.<sup>[15, 123]</sup> However, information on supply days is not typically included in administrative databases in many countries outside the United States, such as in Australia,<sup>[97]</sup> Italy,<sup>[35]</sup> and Denmark;<sup>[111]</sup> estimates of treatment duration based on pack size, strength and quantity dispensed are hindered by the range of possible instructions for use of prescribed opioid. As an alternative, researchers can use a threshold based on the length of episodes of opioid use or the frequency of fills within a time period with or without additional criteria.<sup>[35, 97, 108, 112]</sup>

Although duration measures suffice to determine LTOT, the nature of opioid therapy such as the use of long or short-acting opioids and opioid potency are commonly reported by studies but only included as part of the LTOT definition in seven studies. Similarly, estimating opioid dosage can be challenging, explaining in part the small number of studies using this criteria. This is despite evidence of a dose-dependent association between opioid use and harm with dosages greater than 40-50 mg OMEs, which escalates further with dosages over 90-120 mg OMEs.<sup>[6, 8-10]</sup>

The differences in LTOT definitions and study design resulted in an approximately 300-fold variation on LTOT rates across studies and 13-fold variation in estimates among studies assessing multiple definitions in the same study population.<sup>[24, 26, 52, 59, 79, 99, 123, 126, 128]</sup> This large variability can impair comparisons across jurisdictions and health conditions; and evidence resulting from these studies probably should not be summarised in traditional meta-analysis without careful consideration. Even studies using similar LTOT definitions may vary in terms of the study population and denominator used in the analysis, thus restricting comparisons between studies. We recommend that future studies estimating LTOT from routinely collected data report the information presented in Box 1 to increase the reliability and comparability of findings. Whenever possible, authors should consider conducting a sensitivity analysis to assess the impact of differing LTOT definitions on their estimates.

However, while proportions and the absolute number of people identified as using LTOT across different definitions varies widely, overall trends can be similar when testing definitions in the same study population.<sup>[52, 79, 99, 123]</sup> For instance, a study evaluating three measures of LTOT found all of them were useful in identifying long-term opioid use, with between 0.6%-1.1% of the study population experiencing LTOT use at a given point in time, of which between 68%-84% remained using opioids two years later.<sup>[52]</sup> Similarly, a study defining LTOT as an “Episode of > 90 days supply that began within the first 30 days following opioid index date”<sup>[99]</sup> compared their primary outcome with two other common definitions: 1) > 90 days per year<sup>[135]</sup> and 2) [?] 90 days per year with > 120 days supply dispensed or more than 10 prescriptions filled.<sup>[49]</sup> The authors identified LTOT rates of 20.4% in 2004 and 18.3% in 2011 using the primary definition and results using the first alternative definition were substantially lower (9.4%-8.2%), while the second alternative definition yielded higher results (26.0%-24.5%). However, trends over time remained similar, with reduced LTOT rates in the year 2011 compared to 2004. Another study reported consistent predictors of LTOT despite a high variation on the percentage of patients identified<sup>[123]</sup> replicating definitions from Deyo et al.<sup>[122]</sup> and Shah et al.<sup>[106]</sup>. Yet, these results should be interpreted with caution since only a few studies reported data with sufficient detail to enable the comparison of LTOT rates based on

different measures. In addition, evidence from a systematic review evaluating LTOT in the surgical setting implemented 25 definitions on empirical data and reported a 100-fold variation in results, with low levels of agreement between measures.<sup>[15]</sup>

Undoubtedly, operationalisation definitions should be fit-for-purpose to achieve study aims since LTOT measures have different interpretations and applicability for patients, clinicians, researchers, and payers. For example, rates of LTOT measured at the prescription level are useful to inform patterns of LTOT prescribing and use but give no information on the proportion of patients receiving LTOT. Alternatively, studies reporting LTOT as the proportion of individuals with a specific health condition (the most common in our systematic review) provide useful information for clinicians aiming to identify patients at higher risk of harms and to inform treatment pathways and guidelines. At the payer perspective, LTOT rates estimated as the proportion of patients prescribed opioids or health enrollees allow comparisons across providers. Estimating of rates among the whole population allows comparison of jurisdictions, the evaluation of trends over time and policy interventions impacts. Finally, the level of strictness can identify different groups of LTOT users, with more strict definitions able to identify those at higher risk of harm. <sup>[15, 52]</sup>

### **Box 1: Recommended minimum reporting requirements for studies assessing long-term opioid use based on routinely collected data**

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**1. Opioid ascertainment** Data source for ascertainment (e.g., dispensing, prescribing data) Opioid formulations and doses

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Our systematic review has several limitations. Firstly, we developed a classification of criteria used to define LTOT based on measures of duration or additional criteria. Given the variability and lack of clarity on reporting for some definitions, misclassification could have occurred. However, we minimised misclassification by performing data collection with two independent reviewers. Secondly, since we excluded studies assessing LTOT in surgical settings the results and recommendations drawn from this study may not be applicable for studies assessing LTOT prior or post-surgery. Thirdly, we did not test the performance of different definitions in identifying LTOT users but rather identified those who have been tested to guide future researchers in their choices. Fourthly, we only addressed the completeness of reporting using core items relevant to the operationalisation of LTOT definitions and associated results, identifying key elements that future studies should consider to increase their transparency and reproducibility and did not assess the methodological quality or relevance of included studies.

## **CONCLUSION**

Despite growing interest in evaluating the outcomes of LTOT, there is no harmonised terminology or gold standard definition of LTOT in observational research using routinely collected data. The most common threshold applied was 90 days of supply or use within a year. Definitions were often based on those used in prior research and less often on empirical data, with few studies reporting results according to more than one definition. The appropriateness of definitions employed should be driven by the study aims, the data available, and the strengths and limitations of each measure. Researchers should also consider improving the quality of reporting to allow research transparency, reproducibility, and comparability of findings.

**ACKNOWLEDGEMENTS:** This research is supported by the National Health and Medical Research Council (NHMRC) Centre of Research Excellence in Medicines and Ageing (ID: 1060407) and a Cooperative Research Centre Project (CRC-P) Grant from the Australian Government Department of Industry, Innovation and Science (ID: CRC-P-439). LD is supported by an Australian National Health and Medical Research Council Senior Principal Research Fellowship (APP1135991) and by a US National Institutes of Health grant (R01 DA144740 PI: Degenhardt). The National Drug and Alcohol Research Centre is supported by funding from the Australian Government Department of Health under the Drug and Alcohol Program.

**CONFLICTS OF INTEREST:** The authors report no actual, potential, or perceived conflict of interest with regards to the submission of this manuscript. The Centre for Big Data Research in Health, UNSW Sydney has received funding from AbbVie to conduct research, unrelated to the present study. Allergan did not have any knowledge of, or involvement in, the present study. LD has received untied educational grant funding from Indivior, Mundipharma, Seqirus and Reckitt Benckiser to examine new opioid medications in Australia. These companies had no knowledge of this review.

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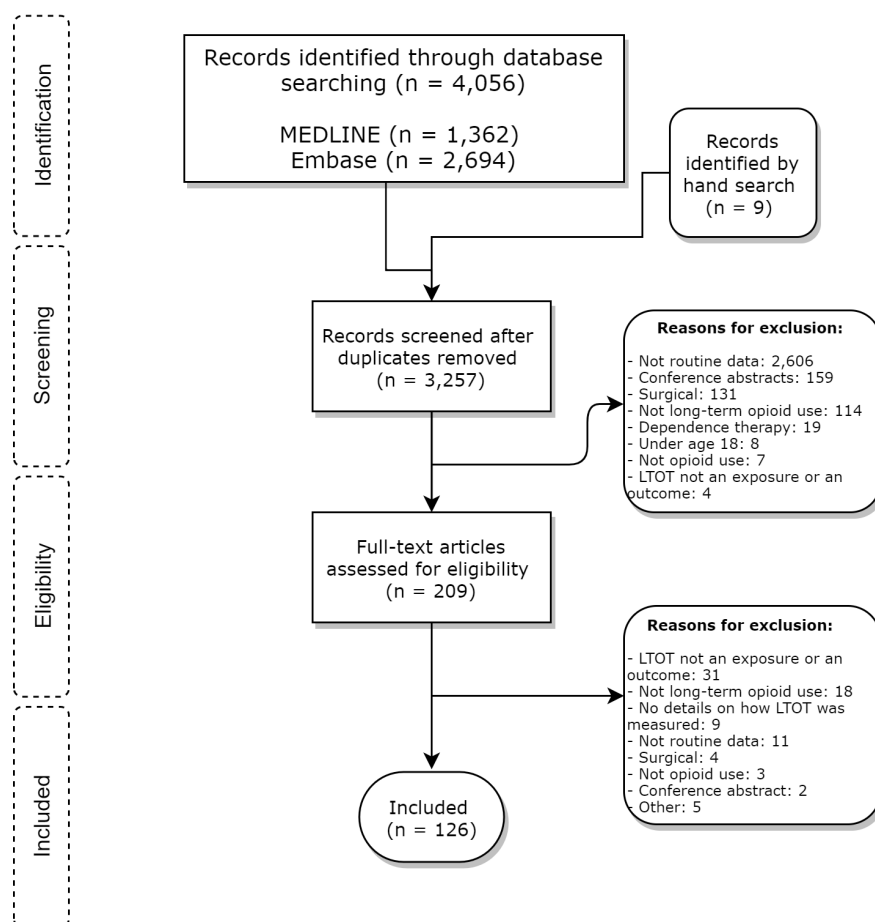
### Figure 1. Flow chart of study selection

**Figure 2. Criteria used to define long-term opioid therapy. A) Number of studies using each criteria B) Sankey diagram showing a two-level combination of criteria used** \*Note: studies can use more than one criteria

### Figure 3. RECORD classification of studies (N=126)

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